Value of the New Bone Classification System for Pediatric Patients with Chronic Kidney Disease

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The 2009 clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD) issued by the global organization Kidney Disease: Improving Global Outcomes (KDIGO) (1) has adopted the previous proposal to use a new definition for the skeletal component of this disorder, namely renal osteodystrophy (2). The new definition emphasizes the usefulness of assessing not only bone turnover (T) but also mineralization (M) and volume (V), the two other key histologic descriptors of bone disease. This more complete evaluation system (TMV system) (Table 1) has been recommended in the interpretation of bone biopsies for all patients with CKD.

KDIGO guidelines are meant to be applicable worldwide. From a clinical perspective, it is important to test whether the recommendations made in a global guideline are effectively applicable to different patient populations with CKD, including children, adults, and elderly individuals; to both genders; to patients with variable kidney diseases and disease courses; and to patients on differing treatment modalities, such as conservative management, dialysis, or kidney transplantation and to which extent they are applicable in various parts of the world. Note that each KDIGO global guideline is designed to provide information and assist decision-making. It is not intended to define a standard of care and should not be construed as one; neither should it be interpreted as prescribing an exclusive course of treatment (1).

In this issue of CJASN, Bakkaloglu et al. (3) report the results of a study of pediatric patients with ESRD to characterize the spectrum of renal osteodystrophy on the basis of the TMV classification system (Table 1). They included in this retrospective, cross-sectional study 161 patients who were on peritoneal dialysis (age 0.7 to 20.0 years) and had undergone bone biopsies for various clinical investigations between 1990 and 2005. This is an extremely large number of bone biopsies, especially considering that bone histomorphometry is only rarely done in children with CKD and that this represents more than 50% of the number of bone biopsies evaluated by the KDIGO CKD-MBD work group (1). Moreover, bone biopsy findings from children who did not have uremia and were of comparable age and ethnic background were available for the sake of comparison. Other positive aspects of the study are that all serum biochemistry measurements were done at the time of bone biopsy sampling, and care was taken to avoid, at least to some degree, interference with previous treatments that might have altered bone histomorphometry findings. Thus, treatment with active vitamin D derivatives was interrupted at least 4 weeks before bone biopsy, and none of the patients had undergone parathyroidectomy within the year before bone biopsy.

The main finding of the report by Bakkaloglu et al. (3) is the demonstration, using classification and regression treat analysis, that both bone turnover and mineralization status can be predicted on the basis of serum intact parathyroid hormone (iPTH), total calcium, and alkaline phosphatase values. Thus, serum iPTH levels of <400 pg/ml, in combination with total alkaline phosphatase values of  <400 IU/ L, provided the highest correct prediction rate for patients with both normal bone turnover and normal mineralization. Levels of PTH were higher and serum calcium levels lower in patients with defective mineralization, irrespective of bone turnover. Of note, the authors identified a large prevalence of previously underecognized mineralization defects in this pediatric dialysis patient cohort.

The question that immediately arises is whether, on the basis of these findings, combinations of serum biochemistry values can provide clinically satisfactory information on bone turnover, mineralization, and volume in the individual patient with CKD. Unfortunately, we are still not there.

The consideration of only four biochemical variables in the study by Bakkaloglu et al. (3) (serum calcium, phosphorus, PTH, and total alkaline phosphatases) may be insufficient for a noninvasive assessment of the TMV system in patients with CKD. No information was available on vitamin D status or serum fibroblast growth factor 23 levels. Total alkaline phosphatase was the only bone-derived parameter measured, with possible limitations as compared with bone-specific alkaline phosphatase. The assay used for the measurement of serum iPTH (IRMA; Nichols Institute Diagnostics, San Clemente, CA) is no longer on the market. Using classification and regression treat analysis, usually a minimum of 80% of correctly identified patients is needed to reach biologic and statistical significance. The levels achieved in this study for correctly identified patients with both normal turnover and mineralization did...
not exceed 72%, and for those with normal bone turnover and defective mineralization, they did not exceed 65%. The long period during which the bone biopsies were taken may have contributed to some heterogeneity in the histomorphometric findings, considering marked changes in treatment strategies over time. It is possible that combining a larger number and/or more specific markers of CKD-marked changes in treatment strategies over time. It is possible that combining a larger number and/or more specific markers of CKD-MBD will allow better discrimination.

Bone volume was not predicted by any of the circulating markers determined by Bakkaloglu et al. (3). This failure may be explained by the limited number of biochemical variables at hand; that none of the pediatric patients with ESRD had low bone volume; and the inclusion of patients with an extremely wide life span, from 1 to 20 years of age. Noninvasive measurements of bone mineral density or volume were not available. The absence of low bone volume and the only exceptional presence of adynamic bone disease is in contrast to previous bone biopsy findings by the same authors of children and adolescents who were on hemodialysis (4) and in stark contrast to reports of adult patients with ESRD (5,6).

Observations made in pediatric patients with CKD may not be sufficient to allow immediate extrapolations to adult patients with CKD, particularly those in the higher age range, who frequently have systemic diseases such as diabetes and osteoporosis, which do not exist in childhood. Of note, Bakkaloglu et al. (3) found a 50% prevalence of mineralization defect, which was higher on average than in the adult ESRD patient population, in whom the prevalence was found to be near 32% (combining adynamic bone disease, osteomalacia, and mixed disease) (1).

Finally, it will also be useful for future studies to analyze cortical bone, in addition to trabecular bone. Changes in the structure and function of cortical bone may be of higher predictive value in terms of fracture than those of trabecular bone (7).

Taken together, Bakkaloglu et al. (3) made the laudable attempt to improve the classification of renal osteodystrophy by a detailed bone histomorphometry analysis that is based on the TMV classification system and its possible prediction using classical serum biochemistry alone remains imperfect. The inclusion of more highly performing markers of bone turnover and mineralization (8,9), together with noninvasive skeletal imaging procedures (10), may allow a better discrimination of the different types of renal osteodystrophy and their significance for patient treatment and outcomes in the future.

Disclosures
None.

References
1. Kidney Disease: Improving Global Outcomes (KDIGO)

See related article, “Value of the New Bone Classification System in Pediatric Renal Osteodystrophy,” on pages 1860–1866.

| Table 1. TMV classification system for renal osteodystrophy |
|-------------|-------------|-------------|
| Turnover    | Mineralization | Volume     |
| Low         | Normal       | Low         |
| Normal      | Normal       | Normal      |
| High        | Abnormal     | High        |

TMV, bone turnover, mineralization, and volume. Reproduced from Moe et al. (reference 2), with permission.